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Geographical Differences in Thromboembolic and Bleeding Risks in Patients with Non-Valvular Atrial Fibrillation: An Ancillary Analysis from the SPORTIF Trials

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Both authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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ABSTRACT

Background: Atrial fibrillation (AF) is associated with an increased risk of stroke, and the use of oral anticoagulation reduces stroke and all-cause mortality. Geographical differences may exist in AF risk factors, risk stratification and treatment strategies.

Methods: A post-hoc subgroup analysis derived from randomized controlled trials, the SPORTIF III and V trials, studying differences between European and North American warfarin-assigned non-valvular AF patients.

Results: Of 3359 patients 41.6% (n=1397) were enrolled in Europe and 1962 (58.4%) from North America. CHA₂DS₂-VASc (p=0.002) and HAS-BLED (p<0.001) scores were higher in North Americans. Good anticoagulation control was more common in North American patients than Europeans.

1-Kaplan-Meier estimate curves show that North Americans had a lower risk of stroke/systemic embolic event (SEE) (p=0.012), but higher risk of myocardial infarction(MI) (p=0.007) and major bleeding (p<0.001), compared to Europeans. Cox multivariate analysis confirmed a lower stroke/SEE risk (p=0.008) and higher MI (p=0.014) and major bleeding risks(p<0.001) in North Americans.

Conclusions: Compared to European AF patients, North Americans had better anticoagulation control and higher thromboembolic and bleeding risk profiles. At follow-up, North American patients had lower stroke/SEE risk but higher MI and major bleeding risks compared to Europeans. Further studies are needed to understand these differences and the discordance between risk profile and lower stroke/SEE rates in North American compared to European patients.

Keywords: atrial fibrillation; thromboembolic risk; bleeding risk; geographical differences.

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1. INTRODUCTION

Atrial fibrillation (AF) epidemiology is constantly changing, and both prevalence and incidence of AF are increasing with projected data showing that in 2020 up to 8.8 million and in 2060, 17.9 million European adult subjects will be diagnosed with AF[1].

The Framingham Heart Study has provided important insights into AF risk factors, clinical characteristics and outcomes[2–4]. More recently published evaluations of the impact of AF on global disease burden show that differences between USA and Europe clearly exist in terms of prevalence, clinical management, anticoagulation use and outcomes occurrence[5,6]. Other observational data, such as the Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation (GLORIA-AF) registry has providing insights into actual differences in management of antithrombotic therapy in the new era of the non-vitamin K antagonist oral anticoagulants (NOACs)[7].

The aims of this analysis were to describe geographical differences between Europe and North America in terms of clinical characteristics and major adverse outcomes from a large cohort of patients with non-valvular AF anticoagulated with warfarin in a randomized controlled trial (RCT) cohort with adjudicated outcome events.

2. METHODS

For the purposes of the present study, we analysed the pooled dataset from the Stroke Prevention using an Oral Thrombin Inhibitor in patients with atrial Fibrillation (SPORTIF) III and V trials. Details on the trial protocol have been reported elsewhere[8].

Outcomes assessment was performed blinded from a central adjudication committee for both the studies.

Anticoagulation control, as reflected by time in therapeutic range (TTR) was calculated according to the standardized Rosendaal interpolation method[9].

Thromboembolic risk was categorised according to CHA₂DS₂-VASc score[10]. Bleeding risk was evaluated according to the HAS-BLED risk score[11].

Details about study design, TTR calculation, risk stratification and outcomes definition have been reported in the Supplementary Materials (Supplementary Methods).

2.1 Statistical Analysis

All continuous variables were tested for normality. Variables with normal distribution were expressed as means and standard deviations (SD). Non-normal distributed variables were expressed as median and interquartile range (IQR). Categorical variables, expressed as counts and percentages, were analysed by chi-squared test. Comparison between distributions of TTR in the two regions was assessed with Kolmogorov-Smirnov (K-S) test.

A linear regression analysis to explore clinical factors significantly associated with TTR according to geographical location was performed. Based on the univariate analysis, all

variables with a p-value <0.10 for the association were entered into the multivariate analysis.

Survival analysis, assessed by an intention-to-treat approach, was performed according geographical location; differences in cumulative risk were analysed using the log-rank test and 1-Kaplan-Meier curves estimates were drafted according to the different groups. Evaluation of clinical characteristics significantly associated with outcomes was explored using a Cox proportional-hazards analysis. All variables considered at baseline were considered for the univariate analyses. All variables with a p-value <0.10 for the association in the univariate analysis, were included into the stepwise multivariate model. Specific Cox models according to both Europe and North America were also performed. A two-sided p value <0.05 was considered statistically significant. All analyses were performed using SPSS v. 22.0 (IBM, NY, USA).

3. RESULTS

Of the 3665 patients originally assigned to the warfarin arm, 3359 (91.6%) of these were randomized either in Europe or North America: 1397 (41.6%) in Europe and 1962 (58.4%) in North America. At baseline (Table 1), patients enrolled in North America were older ($p<0.001$), had a higher BMI ($p<0.001$), with more prevalent paroxysmal AF ($p<0.001$) compared to those enrolled in Europe. Proportion of patients with a creatinine clearance (CrCL) <60 ml/min was higher in North American than in European patients ($p=0.042$).

North America patients had more prior hypertension ($p<0.001$) but good blood pressure control ($<140/90$ mmHg) was more commonly achieved in North America, when compared to Europeans ($p<0.001$). Concomitant diabetes mellitus ($p=0.038$), coronary artery disease [CAD] ($p<0.001$) and chronic heart failure [CHF] ($p=0.005$) were more prevalent in North American patients, as was a previous bleeding episode ($p<0.001$). Conversely, a history of stroke/transient ischemic attack [TIA] was less common in North American patients than Europeans ($p=0.014$). Prior vitamin K antagonist (VKA) use was more common in North American patients than in Europe (<0.001).

Median CHA₂DS₂-VASc score was higher amongst North American patients ($p=0.002$), with a trend for more high thromboembolic risk patients (CHA₂DS₂-VASc score ≥ 2) being enrolled in North America compared to Europe ($p=0.059$). Bleeding risk was higher in North American compared to European patients, both in terms of HAS-BLED score distribution ($p<0.001$) and the proportion with a high bleeding risk profile ($p=0.012$).

3.1 Time in Therapeutic Range (TTR)

As shown in Table 1, median TTR values were similar between Europe and North America ($p=0.893$), but the distribution of TTR values was different among the two geographical regions (Figure 1). In North America, the distribution of TTR tended towards higher values when compared to Europeans (K-S test: 1.597, $p=0.012$).

While no difference was found in the proportion of patients achieving optimal anticoagulation control ($TTR>70\%$) ($p=0.893$), the proportion of patients with poor INR control was lower in North American patients than in Europeans (Table 1), with significant differences being evident for the proportions with $TTR<60\%$ and $TTR<50\%$ ($p=0.003$ and $p=0.007$, respectively).

A regression analysis of the clinical predictors of TTR showed differences between the two geographical regions [Table 2]. In North American patients, female sex ($p=0.001$), concomitant diabetes mellitus ($p=0.015$) and CHF ($p=0.003$) were inversely associated with increasing TTR, while persistent AF ($p=0.001$) and prior VKA use ($p<0.001$) were positively associated with increasing TTR. In European patients, TTR was associated with hypertension ($p=0.012$), particularly with progressively increasing diastolic blood pressures at baseline ($p<0.001$), and prior VKA use ($p<0.001$).

3.2 Follow-Up and Survival

After a median [IQR] follow-up of 576 [500-657] days, there were 81 (2.4%) stroke/SEE events, 49 (1.5%) MI, 118 (3.5%) major bleeds, 192 (5.7%) all-cause deaths and 256 (7.6%)

composite outcome events. Only 7 (0.2%) patients reported haemorrhagic stroke, so no subgroup analysis was performed given the small numbers.

Based on geographical location (Supplementary Table 1), a higher rate of stroke/SEE was found for European patients compared to those enrolled in North America (3.1% vs. 1.9%, respectively; $p=0.019$). Conversely, both myocardial infarction and major bleeding rates were higher in North American patients compared to Europeans (1.9% vs. 0.8%, $p=0.006$ and 4.5% vs. 2.1%, $p<0.001$ respectively). No geographical differences were found in rates of all-cause death and the composite outcome. Similar results were found when considering annualized incidence rates (Supplementary Table 1).

1-Kaplan-Meier estimate curves (Supplementary Figure 1) show that European patients had a higher risk for stroke/SEE (Log-Rank: 6.254, $p=0.012$), while North American patients had a higher risk for MI (Log-Rank: 7.383, $p=0.007$) and major bleeding (Log-Rank: 13.029, $p<0.001$).

3.3 Multivariable Analyses

A Cox regression analyses, according to geographic location, was performed (Supplementary Table 2). In Europe, previous stroke/TIA ($p=0.014$) and CAD ($p<0.001$) were independently associated with the occurrence of Stroke/SEE, while TTR ($p=0.013$) was inversely associated with this endpoint. In North America, only the TTR ($p=0.012$) was inversely associated with Stroke/SEE.

When investigating risk factors associated with MI in Europe, age ($p=0.004$) was only significant risk factor, while in North Americans, both previous stroke/TIA ($p=0.003$) and established CAD ($p=0.001$) were associated with an increased risk for MI, whilst the use of aspirin was inversely associated with MI ($p=0.013$).

Age was independently associated with major bleeding both for Europe and North America ($p=0.045$ and $p=0.001$, respectively) whilst TTR was inversely associated with this endpoint in both geographical regions ($p=0.004$ and $p<0.001$, respectively). Female sex was inversely associated with major bleeding ($p=0.019$) in Europe whilst diabetes mellitus ($p=0.0036$) was also associated with major bleeding in North America.

In the overall cohort, a Cox regression analysis (Table 3) confirmed that European patients had a higher risk for Stroke/SEE ($p=0.008$) compared to North American patients, independent of other concomitant risk factors. In contrast, North American patients had a higher risk for both MI ($p=0.014$) and major bleeding ($p<0.001$), independent of other concomitant risk factors.

3.4 Sensitivity Analysis

A sensitivity analysis was performed using $\text{CrCl}<60$ ml/min as a categorical variable in the Cox regression analysis model (Supplementary Table 3). On univariate analysis $\text{CrCl}<60$ ml/min was associated with both stroke/SEE (hazard ratio [HR]: 2.01, 95% confidence interval [CI]: 1.28-3.15, $p=0.002$) and major bleeding (HR: 1.57, 95% CI: 1.07-2.32, $p=0.021$).

After multivariable regression analysis, $\text{CrCl} < 60 \text{ ml/min}$ was independently associated with stroke/SEE o ($p=0.007$), confirming previous analysis coming from this same dataset[12].

European patients had a higher risk of stroke ($p=0.009$) compared to North Americans, while North American patients had a higher risk for major bleeding ($p<0.001$), independently of a $\text{CrCl} < 60 \text{ ml/min}$.

4. DISCUSSION

In this ancillary analysis from the SPORTIF trials, several differences in risk factors are evident between Europe and in North America amongst non-valvular AF patients. Specifically, North American patients had more comorbidities with associated higher thromboembolic and bleeding risk profiles. North American patients reported a better anticoagulation control management (as reflected by TTR), when compared to Europeans. Despite geographical differences in comorbidities and TTRs, European patients had a higher risk for Stroke/SEE compared to North American patients, whilst the latter had a higher risk for both MI and major bleeding, even after adjusting for confounders on multivariate analysis. These differential risks appear to be independent from a reduced renal function ($\text{CrCl} < 60 \text{ ml/min}$), which is a powerful predictor of both thromboembolic and bleeding risks[12].

Chugh and colleagues have clearly shown how the prevalence of AF in North America has been higher than in Europe over the last 20 years[5]. Despite this, the proportion of deaths attributable to AF has been higher in Europe than in North America, even if North American AF patients had a higher proportion of disability-adjusted life-years (DALYs) compared to Europeans[5]. Rahman et al. have also shown how CAD and CHF are more prevalent concomitant comorbidities in USA than in Europe, compared to either hypertension or diabetes mellitus[6]. In this study, we also confirm the higher prevalence of CAD and CHF in North American AF patients.

Prior studies AF patients in USA have previously reported lower TTR values, ranging from 29%[13] to 62%[14], although anticoagulation clinic based studies have reported slightly higher TTR values (68%)[15]. Conversely, studies from European countries have always showed higher mean TTRs, ranging from 56%[16] to 75%[17]. One observational study, the international study of anticoagulation management (ISAM), clearly showed that patients enrolled in North America had lower TTR values than those enrolled in Europe[18]. A large meta-analysis including data from 69 studies exploring TTR and outcomes in AF patients[19], reported that European patients had mean TTR values that were on average 9.7% (95% CI: 6.0-13.4%) higher than North Americans ($p<0.001$). Interestingly, our data show the converse, that North American patients had a greater proportion of good TTR, in particular TTR>60% and TTR>50%, indicating that within a setting with regular review and follow-up (as in clinical trials), North American AF patients could achieve a good TTR. In contrast, data coming from a subgroup analyses of the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) trial reported no differences in TTR values between North America and Europe[20].

In North American patients, various comorbidities and demographic characteristic were associated with a better TTR while in European patients, hypertension was the main factor associated with TTR. Our observation that diabetes mellitus and CHF were the main clinical factors inversely associated with TTR, is consistent with an ancillary study coming from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) registry, where both comorbidities were associated with a poor TTR[21]. Various clinical comorbidities are known to influence TTR, as incorporated into the SAME-TT₂R₂ score,

which is to aid decision making as to the likelihood of achieving a good TTR (score 0-2) or not (score >2)[22,23]. Of note, determinants of TTR varied between North America and Europe.

Conversely, VKA experienced patients in both regions were more likely to have better anticoagulation control, consistent with previously reported data[19,20].

The evidence of a poorer TTR among European patients could explain why North American patients had a lower risk for Stroke/SEE occurrence, despite having a higher thromboembolic risk profile. The concept that residual risk for adverse outcomes in AF patients is closely related to TTR is strongly supported by current literature, with an inverse relationship between increasing TTR and adverse outcomes[24–26]. Gallagher et al. demonstrated that the proportion of patients free from stroke was proportionally lower with worse TTR[27]. Since North American patients had more comorbidities, physicians may be more likely to monitor and review them more intensively.

Our multivariable analyses suggest that European patients have a higher excess of risk due to previous cerebrovascular and cardiovascular disease, whilst North American patients may have had better management of comorbidities, as well as better TTR. Of note, TTR was consistently important, being inversely related to bleeding risk irrespective of geographical region. Despite the higher comorbidities in North America, adverse outcomes differed, with European patients having a higher risk for Stroke/SEE whilst North American patients had a higher risk for both MI and major bleeding. These differential expressions of adverse outcomes merit further study.

4.1 Limitations

The major limitation to this paper is clearly its post-hoc ancillary nature, as well as the study design that enrolled separately in North America and Europe patients for the SPORTIF V and SPORTIF III trials, respectively. Trial designs were also different where SPORTIF V was a double-blind double dummy trial, whilst SPORTIF III was open-label, even if both inclusion and exclusion criteria were exactly the same in both studies. Since the presented subgroups were not pre-specified, our results could be based on a limited power and partially limit their generalizability. Our hypothesis focuses on geographical differences rather than ethnic differences, which would require a separate analysis given the many different ethnicities in North America and Europe. Also, data about concomitant medications such as statins and others, that could interact with mortality risk, were not available for this analysis. Furthermore, no other measures of anticoagulation control were available, in order to verify our findings. Finally, the trial data and population reflected practice nearly ten years ago, and may not precisely reflect current epidemiology and clinical practice. Nonetheless, our data have to be considered hypothesis-generating. Differences that we underlined should be taken into consideration for future studies, also focusing on ethnic differences whenever possible, to assess if real differences exist in terms of excess risk among European and North American populations.

5. CONCLUSIONS

North American AF patients, when compared to European ones, had better anticoagulation control, higher thromboembolic and bleeding risk profiles. At follow-up, North American patients had lower stroke/SEE rates but higher myocardial infarction and major bleeding rates compared to Europeans. Further studies are needed to understand the geographical

differences in high event rates amongst AF patients, and the discord between high risk profile and lower stroke/thromboembolism rates in North American compared to European patients with AF.

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Table 1: Baseline characteristics according to geographic region

	Europe	North America	p
	N= 1397	N= 1962	
Age years , median [IQR]	71 [66-76]	73 [66-78]	<0.001
Female Sex , n (%)	436 (31.2)	609 (31.0)	0.916
BMI kg/m² , median [IQR] 3345	28.1 [25.2-31.1]	28.5 [25.4-32.9]	<0.001
CrCl ml/min , median [IQR] 3342	81.1 [61.6-103.5]	79.3 [59.2-103.9]	0.219
CrCl<60 ml/min , n (%)	317 (22.9)	507 (25.9)	0.042
Blood Pressure <140/90 mmHg , n (%)	531 (38.1)	1160 (59.3)	<0.001
Type of AF , n (%)			<0.001
<i>Paroxysmal AF</i>	108 (7.7)	270 (13.8)	
<i>Persistent AF</i>	1289 (92.3)	1690 (86.2)	
Hypertension , n (%)	1014 (72.6)	1582 (80.6)	<0.001
Diabetes Mellitus , n (%)	301 (21.5)	483 (24.6)	0.038
Current Smoking , n (%)	132 (9.4)	165 (8.4)	0.296
Coronary Artery Disease , n (%)	560 (40.1)	944 (48.1)	<0.001
Previous Stroke/TIA , n (%)	295 (21.1)	348 (17.7)	0.014
Chronic Heart Failure , n (%)	494 (35.4)	788 (40.2)	0.005
Previous Bleeding , n (%)	55 (3.9)	140 (7.1)	<0.001
Concomitant Aspirin Use , n (%)	281 (20.1)	367 (18.7)	0.308
Prior VKA Use , n (%)	993 (71.1)	1667 (84.7)	<0.001
CHA₂DS₂-VASc , median [IQR]	3 [2-4]	3 [2-4]	0.002
Thromboembolic Risk , n (%)			0.059

<i>Low</i>	2 (0.1)	4 (0.2)	
<i>Medium</i>	203 (14.5)	231 (11.8)	
<i>High</i>	1192 (85.3)	1727 (88.0)	
HAS-BLED , median [IQR] 3302	3 [2-4]	3 [2-4]	<0.001
0-2, n (%)	433 (31.4)	526 (27.4)	0.012
≥3, n (%)	947 (68.6)	1396 (72.6)	
<i>Time in Therapeutic Range 3318</i>			
TTR % , median [IQR]	68.5 [54.5-80.5]	69.0 [57.2-79.1]	0.473
TTR>70% , n (%)	657 (47.3)	917 (47.5)	0.893
TTR<65% , n (%)	600 (43.2)	776 (40.2)	0.087
TTR<60% , n (%)	486 (35.0)	582 (30.2)	0.003
TTR<50% , n (%)	257 (18.5)	289 (15.0)	0.007

Legend: AF= atrial fibrillation; BMI= body mass index; CHA₂DS₂-VASc= congestive heart failure, hypertension, age≥75 years, diabetes mellitus, stroke/TIA, vascular disease, age 65-74 years, sex category; CrCl= creatinine clearance; HAS-BLED= hypertension, abnormal renal and liver function, stroke, bleeding, labile INR, elderly, drugs or alcohol; IQR= interquartile range; TIA= transient ischemic attack; TTR= time in therapeutic range; VKA= vitamin K antagonist.

Table 2: Regression analysis for clinical predictors of time in therapeutic range according to geographic region

	Beta	95% CI	T	p
<u>Europe</u>				
Hypertension	-3.084	-5.487 - -0.682	-2.519	0.012
DBP at Baseline (<i>per mmHg</i>)	0.197	0.087-0.306	3.527	<0.001
Prior VKA Use	7.484	5.226-9.743	6.500	<0.001
<u>North America</u>				
Female Sex	-2.861	-4.504 - -1.219	-3.417	0.001
Persistent AF	3.656	1.451-5.861	3.252	0.001
Diabetes Mellitus	-2.189	-3.956 - -0.423	-2.431	0.015
Chronic Heart Failure	-2.352	-3.909 - -0.794	-2.961	0.003
Prior VKA Use	6.187	4.086-8.289	5.773	<0.001

Legend: AF= atrial fibrillation; CrCl= creatinine clearance; DBP= diastolic blood pressure;

VKA= vitamin K antagonist.

Table 3: Cox multivariable regression analysis for study outcome in the overall population

	HR	95% CI	p
<i>i) Stroke/SEE</i>			
Previous Stroke/TIA	1.91	1.18-3.09	0.009
Coronary Artery Disease	1.78	1.13-2.81	0.013
TTR (%)	0.98	0.97-0.99	0.001
North America (vs. Europe)	0.55	0.35-0.86	0.008
<i>ii) Myocardial Infarction</i>			
Previous Stroke/TIA	2.58	1.42-4.67	0.002
Coronary Artery Disease	3.26	1.74-6.10	<0.001
Concomitant Aspirin Use	0.27	0.10-0.76	0.013
North America (vs. Europe)	2.34	1.19-4.59	0.014
<i>iii) Major Bleeding</i>			
Age (per year)	1.05	1.02-1.07	<0.001
Female Sex	0.65	0.42-0.98	0.041
TTR (%)	0.98	0.97-0.98	<0.001
North America (vs. Europe)	2.15	1.41-3.27	<0.001

Legend: SEE= systemic embolic event; TIA= transient ischemic attack; TTR= time in therapeutic range.

FIGURE LEGENDS

Figure 1: Distribution of time in therapeutic range according to geographic region

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DECLARATION OF CONFLICTING INTERESTS

MP has been consultant for Boehringer Ingelheim.

GYHL has been consultant for Bayer/Janssen, Astellas, Merck, Sanofi, BMS/Pfizer, Biotronik, Medtronic, Portola, Boehringer Ingelheim, Microlife and Daiichi-Sankyo. Speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche and Daiichi-Sankyo.

AUTHOR CONTRIBUTIONS

MP and GYHL conceived the study, analysed and interpreted data, drafted and revised the manuscript. MP and GYHL have full access to data and take full responsibility for manuscript content.

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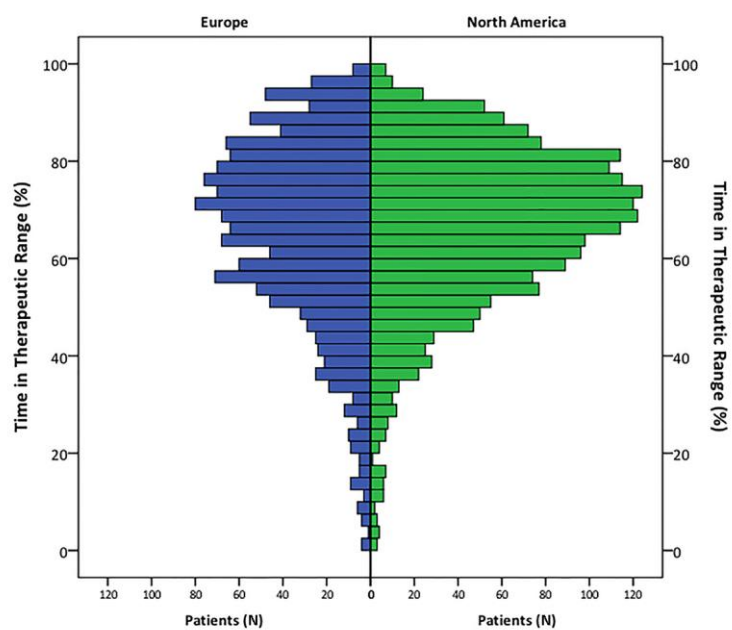


Figure 1